REMARKS

Applicants request entry of this Amendment and reconsideration of the rejection of the claims.

Applicants have amended claims 25 and 29. Applicants submit the claims as amended are supported throughout the specification including at page 11, lines 32-35. Applicants submit the claims as amended do not raise any issues of new matter.

Applicants have added new claims 38-42. Applicants submit the newly presented claims are supported throughout the specification including at page 7, line 32 to page 8, line 8; page 11, lines 32-35; and page 16, lines 4-27. Applicants submit the new claims do not raise any issues of new matter.

Claim Rejections - 35 U.S.C. §112

Claim 29 is objected to under 37 CFR 1.75(c), as being of improper dependent for failing to further limit the subject matter of a previous claim.

The Examiner contends that the claim fails to further limit the independent claim 25. Applicants have amended claim 25 and submit the amendment to the claim obviates the objection. Applicants request withdrawal of objection.

Claim 25 and 29 were rejected as indefinite for reciting "homogenous as to the heavy chain C-terminal amino acid residue" in claim 25. Dependent claim 29 recites that the C-terminal amino acid sequence comprises Cys-Ala-Ala.

The Examiner contends that the claims are unclear in the recitation of "homogeneous as to the heavy chain C-terminal amino acid residue". Applicants submit that claim 25 as amended obviates the rejection. Applicants respectfully request withdrawal of the rejection.

Claim Rejections - 35 U.S.C. §102

Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Rhind S.K. (WO 90/09196, 8/23/1990).

The Examiner contends that Rhind et al. teaches a monospecific $F(ab')_2$ with only one hinge region cysteine which is used to form a non-disulphide bridge and, therefore, anticipate Applicants' claims. Applicants respectfully traverse.

Applicants claims are directed to $F(ab')_2$, wherein each Fab' comprises a CH1 domain fused to an amino acid sequence Cys-X-X, wherein the cysteine forms a disulfide bond to form the $F(ab')_2$.

Applicants submit that Rhind et al. does not teach or suggest a $F(ab')_2$, wherein each Fab' comprises a CH1 domain fused to an amino acid sequence Cys X X, wherein the cysteine form a disulfide bond to form the $F(ab')_2$. Rhind et al. discloses a $F(ab')_2$ having an inter heavy chain non-disulfide bond and specifically excludes formation of disulfide bonds. Thus, Applicants submit that for at least these reasons, Rhind does not anticipate Applicants' claimed invention. Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection.

Claim Rejections - 35 U.S.C. §103

Claims 25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhind S.K. (WO 90/09196, 8/23/1990) in view of Cunningham et al (Science, 244 (4908): 1081-1085, 6/2/1989).

The Examiner contends that Rhind et al. teaches a $F(ab')_2$ that has only one hinge region cysteine and is homogeneous to the C-terminal amino acid, but does not specifically teach the C-terminal amino acid sequence Cys-Ala-Ala. The Examiner further contends that Cunningham et al. teaches the desirability of alanine substitutions and asserts it would be prima facie obvious to combine the teachings of Rhind et al. with those of Cunningham et al. to form a $F(ab')_2$ with only one hinge region cysteine and a C-terminal amino acid sequence Cys-Ala-Ala. Applicants respectfully traverse.

Applicants submit that in order to establish a prima facie case of obviousness, the Examiner must establish that the cited references when combined disclose all of the elements of the claims, that one of skill in the art would be motivated to combine the references and the references when combined would provide a reasonable expectation of success. Applicants submit the Examiner has not established a prima facie case of obviousness in the least because the references when combined do not teach or suggest all of the elements of the claims and one of skill in the art would not be motivated to combine the references cited by the Examiner.

Applicants' claims are directed to a $F(ab')_2$ wherein each F(ab') comprises a CH1 domain fused to an amino acid sequence Cys-X-X, wherein X is Ala, Arg, Asp or Pro, and wherein the cysteine forms a disulfide bond to form the $F(ab')_2$.

Applicants submit that Rhind et al. alone or combined with Cunningham et al. do not teach or suggest all of the elements of Applicants' claims. Rhind et al. is directed to forming antibody molecules or fragments that are connected by a non-disulfide bond bridging group useful to attach reporter molecules or other types of groups to the bridging molecules. Rhind et al. specifically excludes antibody molecules or fragments having interheavy chain disulfide bonds. Applicants' claims now provide that a cysteine residue of each Fab' forms a disulfide bond to form the $F(ab')_2$.

Moreover, Rhind et al. does not teach or suggest a Fab' comprising a CH1 domain fused to an amino acid sequence Cys-X-X, wherein X is Ala, Arg, Pro or Asp. The Rhind et al. reference discusses altering hinge regions or substituting one type of hinge region for another. This reference does not teach or suggest that a Fab' comprising a CH1 domain fused to amino acid sequence Cys-X-X can or should be formed to provide for formation of $F(ab')_2$.

The deficiencies of the Rhind et al. reference are not remedied by reference to the Cunningham et al. reference. The Cunningham et al. reference does not discuss antibodies or fragments and is directed to alteration of human growth hormone. The Cunningham et al. reference merely teaches the desirability of making alanine substitutions in polypeptides to identify amino acids that are important in the function of the protein. This reference does not teach or suggest a Fab' comprising a CH1 domain fused to an amino acid sequence Cys-X-X, wherein X is Ala, Arg, Asp or Pro, and wherein the cysteine forms a disulfide bond to form the $F(ab')_2$. Thus, even when Rhind et al. is combined with Cunningham, the references do not disclose all of the elements of the claimed invention.

Furthermore, Applicants submit that one of skill in the art would not be motivated to combine these references as they are directed to solving totally different problems. The Rhind et al. reference is directed to a method for forming antibodies or fragments thereof that have non-disulfide bridges between the heavy chains. Cunningham et al. is directed to studying human growth hormone and using alanine substitution at certain positions to decrease function of the protein in order to map residue positions important to the function of the molecule. Thus, one of

skill in the art would not be motivated by Cunningham to make alanine substitutions in the antibodies of Rhind et al unless they were trying to make the residues important to function of the molecule. Thus, Applicants submit one of skill in the art would not be motivated to combine these references.

Thus, Applicants request withdrawal of the 35 U.S.C. § 103 rejection on this basis.

The Examiner also rejected claims 25 and 29 under 35 U.S.C. § 103(a) as being unpatentable over Glennie et al. in view of Wahl and Cunningham. The Examiner contends that Glennie et al. teaches a $F(ab')_2$ containing thioether linked Fab fragments coupled through a single hinge region cysteinyl sulfur, but does not teach a monospecific $F(ab')_2$ or a homogeneous heavy chain C-terminal amino acid sequence of Cys-Ala-Ala. The Examiner further contends that $F(ab')_2$ with a C-terminal sequence of Cys-Ala-Ala are taught by Wahl and Cunningham. Applicants respectfully traverse.

As discussed previously, Applicants' claims are directed to a $F(ab')_2$ wherein each Fab' comprises a CH1 domain fused to an amino acid sequence Cys-X-X, wherein X is Ala, Arg, Pro or Asp, and the cysteine forms a disulfide bond to form the $F(ab')_2$.

The Glennie et al. reference is directed to using a bispecific $F(ab')_2$ molecule using a $F(ab')_2$ that is prepared by proteolytic digestion, followed by reduction to F(ab') followed by modification of SH groups with a bifunctional crosslinking reagent. The Glennie et al. reference alone or in combination does not disclose all of the elements of Applicants' claims. The Glennie et al. reference does not disclose a $F(ab')_2$ free of hinge region intrachain disulfide bonds. In Figure 8, the Glennie et al. reference indicates that in at least one of the F(ab') molecules the two other SH groups are bonded intramolecularly. See Figure 8 and p. 2373, col. 2, paragraph 3.

Moreover, Glennie et al. does not teach or suggest a Fab' comprising a CH1 domain fused to an amino acid sequence Cys-X-X, wherein X is Ala, Arg, Pro or Asp. The Glennie et al. reference does not discuss altering the hinge region or number of cysteines available for crosslinking. This reference does not teach or suggest that a Fab' comprising a CH1 domain fused to amino acid sequence Cys-X-X can or should be formed to provide for formation of $F(ab')_2$.

The deficiencies of Glennie et al. are not remedied by reference or combination with either Wahl or Cunningham. There is no teaching or suggestion in Wahl of a F(ab') comprising

a CH1 fused to a Cys-X-X sequence, wherein X is Ala, Arg, Asp or Pro, and wherein the cysteine forms a disulfide bond to form $F(ab')_2$. Cunningham et al. does not even discuss antibodies and discloses a method of substituting amino acid residues with alanine to determine residues that when substituted with alanine disrupt function of the molecule, and thus does not disclose any of the characteristics of $F(ab')_2$ as claimed. Thus, even when combined these references do not disclose all of the elements of Applicants' invention.

Moreover, there would be no motivation to combine these references as they are directed to solving totally different problems. The Glennie et al. reference is directed to forming a bispecific $F(ab')_2$ with different specificity using a crosslinking agent. The Wahl et al. reference is directed to forming a monospecific $F(ab')_2$ using proteolytic digestion. Because Wahl et al. is directed to a monospecific $F(ab')_2$ several steps of the process of Glennie et al. are not necessary and would diminish yield of $F(ab')_2$. Cunningham does not even discuss antibodies or antibody fragments and discusses use of alanine substitution to disrupt function of the molecule and not to enhance or improve function of the molecule. Thus, one of skill in the art would not combine these references to making Applicants' claimed invention obvious.

Based on the foregoing, Applicants submit that the claimed invention is not obvious in view of Glennie et al in view of Wahl et al. and Cunningham et al., because even if combined these references do not disclose all of the elements of the claimed invention and there would be no motivation to combine these references. Applicants respectfully request withdrawal of the rejection.

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Amdt. dated January 7, 2005
Reply to Office Action of July 9, 2004

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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